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PATENT

Attorney Docket No. A-70204-1/RMS/AXG/JML

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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In re application of:

Vi-En CHOONG, et al.

Serial No.: 09/840,000

Filing Date: 19 April 2001

For: **Method for enhancing nucleic acid hybridization** (as amended)

Examiner: Bradley L. Sisson

AUG 08 2002

Group Art Unit: 1634

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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail addressed to the Assistant Commissioner of Patents, Washington, D.C. 20231 on 29 July 2002.

Signed

*Todd V. Leone*  
Todd V. LEONE

AMENDMENT

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Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

Following is Applicants' response to the Office Action mailed 29 March 2002. A Petition for a one-month extension of time is enclosed, together with the appropriate fee. This response is mailed on or before the extended deadline of 29 July 2002, making this a timely response. Please amend the application as follows:

IN THE SPECIFICATION

Please insert the following paragraph as the first sentence of the specification:

B<sup>1</sup> - This application is a continuation of Application Number 09/503,163, filed May 4, 1999, now U.S. Patent Number 6,238,909. -

Please replace the title of the application with:

Method for enhancing nucleic acid hybridization

IN THE CLAIMS

Please add the following new claim 28:

B<sub>2</sub> 28. (New) A method for enhancing nucleic acid hybridization in a device having one or a plurality of microlocation(s), each microlocation comprising a nucleic acid probe present on a substrate, said method comprising:

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(a) applying a sample comprising one or more nucleic acids to said microlocation(s); and  
(b) placing said device between two or more electrodes such that an electric field is generated at said microlocation(s), and such that said one or more nucleic acids are transported to said nucleic acid probes present at said microlocation(s) under conditions sufficient for hybridization to occur.

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#### REMARKS

This Amendment and Response is submitted in response to the Office Action mailed 29 March 2002. Withdrawal of the rejection and reconsideration with an eye toward allowance is respectfully requested. For the Examiner's convenience, a clean copy of all pending claims is attached, entitled "Appendix A: Pending Claims".

#### Status of the Claims

Claims 15-19, 21-24, 26, and 27-28 are pending in the application, claim 28 having been added by this amendment. Claims 15-19, 21-24, 26, and 27 stand rejected. Support for new claim 28 can be found throughout the originally filed specification, claims and drawings. For example, in originally filed claim 15 and page 16, lines 29-32 and page 17, lines 1-2. Thus, no new matter is presented, and entry of the amendment is respectfully requested.

#### Priority

An appropriate priority reference is inserted as the first sentence of the specification. Applicants trust that the claim for priority to Application Number 09/503,163, now U.S. Patent Number 6,238,909 has been perfected.

#### Specification

The title of the application has been amended to read "Method for enhancing nucleic acid hybridization". Applicants submit that the amendment addresses the Examiner's concerns.

#### Claim Rejections - 35 U.S.C. §102

Claims 15, 17-19, and 22-24 were rejected under 35 U.S.C. §102(b) as being anticipated by Okano, et al. (U.S. Patent Number 5,434,049).

Okano discloses the elution of polynucleotides by the application of an electric field. Probes are immobilized on a plurality of cells, each including a separation electrode. A counter electrode is placed adjacent to each separation electrode. These electrodes clearly contact the sample solution when in use (see Okano, Figs. 5 and 6, and col. 9, lines 49 - col. 10, line 24). Sample containing target polynucleotides is added, and hybridization takes place in a conventional manner (see col. 6, lines 12-30). That is, target polynucleotides are transported to immobilized probes primarily via diffusion. Okano discloses the use of an electric field to elute hybridized polynucleotides from one or more selected cells

(see col. 2 and col. 10). Cells with positively charged separation electrodes retain their hybridized polynucleotides while polynucleotides are eluted from cells having a negatively-charged separation electrode.

In contrast, Applicants disclose a method for enhancing hybridization of nucleic acids through the use of an electric field. As shown in Applicants' Figs. 1 and 3, as well as on page 11, lines 10-25, an electric field is generated at one or more microlocations by electrodes that are not in contact with the sample solution. Therefore, no current is generated in the microlocations. Nucleic acids are manipulated via electrostatic manipulation in such a way as to increase the occurrence of hybridization.

As the Examiner is aware, for a reference to anticipate a claim, the reference must teach every element of the claim (see M.P.E.P §2131).

Applicants respectfully submit that Okano fails to teach or suggest all limitations of Applicants' independent claims 15 and 22, including "applying charge to said device to produce an electric field at said microlocation(s) without creating current flow in said microlocation(s)". Okano recites electrodes in contact with the sample solution, as shown in Okano Figs. 5 and 6. Thus, the application of a voltage between these electrodes would necessarily interact with the sample solution, generating current flow. Further, Okano fails to teach or suggest the application of charge "such that said one or more nucleic acids are transported to said nucleic acid probes present at said microlocation(s) under conditions sufficient for hybridization to occur". Rather, as discussed above, Okano teaches the application of charge such that polynucleotides are eluted from a location within a device.

Claims 17-19, and 23-24 depend from and include all limitations of base claims 15 and 22, respectively. Accordingly, Applicants respectfully submit that the 35 U.S.C. §102(b) rejection of claims 15, 17-19, and 22-24 as being anticipated by Okano is improper, and should be withdrawn.

#### **Claim Rejections - 35 U.S.C. §103**

Claims 15-19, 21-24, 26, and 27 were rejected under 35 U.S.C. §103(a) as being unpatentable over Okano et al., in view of Lizardi (U.S. Patent Number 5,059,294).

Okano is discussed above.

Lizardi is directed toward a method for separating nucleic acids and nucleic acid probes (see abstract and col. 2, lines 60-63). Sample containing hybridized probes and non-specifically bound complexes is brought into contact with a support medium. The application of an alternating electrical field results in the separation of the non-specifically bound complexes.

As discussed above, in contrast to both Okano and Lizardi, Applicants disclose the use of an electric field to enhance nucleic acid hybridization.

As the Examiner is aware, to establish *prima facie* obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. (See M.P.E.P. §2142).

Applicants submit that Okano and Lizardi, taken alone or in combination, fail to disclose or suggest all limitations of Applicants' independent claims 15 and 22 including "applying charge to said

device to produce an electric field at said microlocation(s) without creating current flow in said microlocation(s)" and the application of charge "such that said one or more nucleic acids are transported to said nucleic acid probes present at said microlocation(s) under conditions sufficient for hybridization to occur".

Claims 16-19 and 21 depend from and include all limitations of base claim 15. Claims 23-24, 26, and 27 depend from and include all limitations of base claim 22. Accordingly, Applicants submit that the 35 U.S. C. §103(a) rejection of claims 15-19, 21-24, 26, and 27 over Okano in view of Lizardi is improper, and should be withdrawn.

#### **New Claim**

Applicant has added new claim 28 which further distinguishes over the cited art. For example, claim 29 further requires "placing said device between two or more electrodes such that an electric field is generated at said microlocation(s), and such that said one or more nucleic acids are transported to said nucleic acid probes present at said microlocation(s) under conditions sufficient for hybridization to occur". The cited art fails to disclose or suggest these features.

#### **CONCLUSION**

Applicants submit that the claims are in condition for allowance, and early notification of such is earnestly solicited. The Examiner is invited to telephone the undersigned attorney in the event that further issues are identified that would preclude allowance of the claims. While Applicant believes that no further fees are due at this time, the Commissioner is authorized to charge any fees that may be due as a result of filing this amendment, including additional claims fees not already paid for, or other fees that have not been separately paid, to Deposit Account 50-2319 (Order No. 469008-00160 [A-70204-1]).

Respectfully submitted,

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## **Appendix A: Pending Claims**

15. A method for enhancing nucleic acid hybridization in a device having one or a plurality of microlocation(s), each microlocation comprising a nucleic acid probe present on a substrate, said method comprising the steps of:

- (a) applying sample comprising one or more nucleic acids to said microlocation(s); and
- (b) applying charge to said device to produce an electric field at said microlocation(s) without creating current flow in said microlocation(s), and such that said one or more nucleic acids are transported to said nucleic acid probes present at said microlocation(s) under conditions sufficient for hybridization to occur.

16. The method of claim 15, wherein said microlocation(s) comprise a porous media.

17. The method of claim 15, which comprises the further step (c) of applying charge to said device to produce an electric field at said microlocation(s) without creating current flow in said microlocation(s), and such that said one or more nucleic acids that are not hybridized with said nucleic acid probes are transported away from said nucleic acid probes at said microlocation(s).

18. The method of claim 17, wherein steps (b) and (c) are repeated at least once.

19. The method of claim 15, said device comprises a plurality of microlocations, wherein said microlocations each comprise a nucleic acid probe having known binding characteristics, and wherein the nucleic acid probe present at one microlocation differs from the nucleic acid probe present at other microlocations in a known and predetermined manner.

21. The method of claim 15, wherein charge is applied to said device in such a way as to produce a stirring or mixing motion, or cause a rotational motion at said microlocation(s).

22. A method for enhancing nucleic acid hybridization in a device having one or a plurality of microlocation(s) present on a substrate, each microlocation comprising a nucleic acid probe, said method comprising the steps of:

- (a) applying sample comprising one or more nucleic acids to said microlocation(s);
- (b) applying charge to said device to produce an electric field at said microlocation(s) without creating current flow in said microlocation(s), and such that said one or more nucleic acids are transported to said nucleic acid probes at said microlocation(s) under conditions sufficient for hybridization to occur; and
- (c) applying charge to said device to produce an electric field at said microlocation(s) without creating current flow in said microlocation(s), and such that said one or more nucleic acids that are not

hybridized with said nucleic acid probes are transported away from said nucleic acid probes at said microlocation(s).

23. The method of claim 22, wherein steps (b) and (c) are repeated at least once.

24. The method of claim 22, said device comprising a plurality of microlocations, wherein said microlocations each comprise a nucleic acid probe having known binding characteristics, and wherein the nucleic acid probe present at one microlocation differs from the nucleic acid probe present at other microlocations in a known and predetermined manner.

26. The method of claim 22, wherein said microlocation(s) comprise a porous media.

27. The method of claim 22, wherein charge is applied to said device in such a way as to produce a stirring or mixing motion, or cause a rotational motion at said microlocation(s).

28. (New) A method for enhancing nucleic acid hybridization in a device having one or a plurality of microlocation(s), each microlocation comprising a nucleic acid probe present on a substrate, said method comprising:

- (a) applying a sample comprising one or more nucleic acids to said microlocation(s); and
- (b) placing said device between two or more electrodes such that an electric field is generated at said microlocation(s), and such that said one or more nucleic acids are transported to said nucleic acid probes present at said microlocation(s) under conditions sufficient for hybridization to occur.